IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Gadde, et al.
Appl. No.	:	10/830,071
Filed	:	April 23, 2004
For	:	METHOD FOR TREATING OBESITY
Examiner	:	Henley III, Raymond J.
Group Art Unit	:	1614
Confirmation No.	:	7687

DECLARATION OF K. RANGA R. KRISHNAN, M.D. UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, K. Ranga R. Krishnan, M.D., a named inventor of the above-captioned application, based on personal knowledge or information, declare and state as follows:

1. I am a co-inventor of the subject matter claimed in the above-captioned application.

2. I understand that certain claims of the above-captioned application are being rejected as anticipated by Jennings, U.S. Patent Publication No. 2004/0029941. I am informed that the Jennings Application was initially assigned to Elan Pharmaceuticals, Inc., which later transferred assignment of the application to Eisai, Inc., the current assignee of the Jennings Application.

3. Over the years, studies have been conducted on zonisamide in epileptic patients. My co-inventor and I developed an interest in using zonisamide as a weight loss agent to treat obesity, a condition characterized by an excess of body fat.

4. On or about August 31, 2000, representatives of Elan met with me to discuss zonisamide for use in treating bipolar disorder, a psychiatric condition. During this meeting, I advised the Elan representatives that zonisamide had the potential to be a good antiobesity drug.

5. On or about September 7, 2000, my co-inventor, Dr. Gadde, submitted a proposal by Dr. Gadde and me to Elan that described a proposed clinical study at Duke University ("the Duke Study") for treating obese patients with zonisamide. A true and correct copy of this proposal is attached hereto as Exhibit A. The Duke Study proposal included background

information on obesity, identified objectives for the study, proposed a study design, and described specific criteria for including and excluding particular groups of patients in the study population. This proposal was submitted to Elan to see if Elan would be interested in funding the Duke Study and/or in providing zonisamide samples for the study.

6. In October 2000, a revised version of the Duke Study proposal was submitted to Elan. A true and correct copy of this revised proposal is attached hereto as Exhibit B. After receiving the revised proposal, Elan provided Duke with unrestricted funding and samples of zonisamide that were used to conduct the Duke Study. A true and correct copy of a third revision of the protocol from the Duke Study that Dr. Gadde provided to Elan is attached as Exhibit C. I am not aware of any material transfer agreement, or any other agreement of any kind, written or oral, between Duke and Elan regarding the Duke Study, nor any request or receipt by Elan of intellectual property rights or any other rights to the data and materials generated in the course of the Duke Study.

7. The Duke Study described in the proposals was conducted at Duke University Medical Center by Duke personnel from approximately March 2001 until approximately March 2002. In December 2001, Dr. Gadde prepared an abstract describing the initial results of the Duke Study and submitted it to Elan as a courtesy, prior to publication of the abstract. A true and correct copy of this abstract is attached hereto as Exhibit D. In March 2002, Dr. Gadde informed Elan that the abstract would be presented in May 2002 at the meeting of the American Psychiatric Association ("APA").

8. At the request of Julianne E. Jennings, an Elan product manager and sole named inventor of the Jennings Application, a telephone call was held in late April, 2002, with Ms. Jennings and Mr. J. Mark Hoch of Elan, and Dr. Gadde. It was later learned that Hoch was a patent attorney for Elan. During the telephone call, Dr. Gadde answered Elan's questions and provided detailed information regarding the use of zonisamide to treat obesity as well as other conditions, such as binge eating disorder and bulimia.

9. Without informing Duke, Elan filed a provisional patent application on May 6, 2002, with the U.S. Patent and Trademark Office relating to the use of zonisamide for weight loss treatment. This application was assigned Provisional Application Serial No. 60/378,446. On May 2, 2003, U.S. Patent Application No. 10/429,474 was filed, claiming priority to provisional application 60/378,446. The 10/429,474 application published on February 12, 2004 as U.S. Patent Publication No. 2004/0029941, which is the Jennings Application.

10. Most of the substantive information contained in the Jennings Application was provided by Dr. Gadde, in writing or orally. Substantial portions of the Elan Application consist of statements that were copied verbatim from the proposals and abstracts provided to Elan by Dr. Gadde. Of particular note is the fact that the results and conclusion sections of the sole example in the Jennings Application is copied directly from the abstract of the Duke Study results. None of the experimental work described in Example 1 of the Jennings Application was conducted by Jennings or assignees Elan and Eisai.

11. On May 17, 2002, prior to publication of the Duke Study abstract at the APA meeting, Duke filed a provisional patent application with the PTO disclosing the use of

zonisamide and other compounds for treating weight loss. This application was assigned Provisional Application Serial No. 60/380,874. U.S. Patent Application No. 10/440,404, the parent of the above-captioned application, was filed May 19, 2003, claiming priority to provisional application 60/380,874. The inventors named on the Duke Application are Drs. Gadde and Krishnan.

12. The evidence attached demonstrates that my co-inventor and I conceived of and reduced to practice the claimed subject matter prior to the filing date of the Jennings Application, and diligently filed a patent application thereafter. The exhibits also demonstrate that the information in the Jennings Application disclosing the claimed invention of the above-captioned application is derived from us. Thus, to the extent that the Jennings Application describes our claimed invention, it is a description of our own previous work. As such, the Jennings Application does not constitute disclosure of the claimed invention by another prior to the invention thereof by us.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

By: _____ Date: 11/14/07
K. Ranga R. Krishnan, M.D.

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EXHIBIT A

Proposal presented to Elan Pharma on the 7th September, 2000 by:
Kishore M. Gadde, MD 919-668-0208 gadde001@mc.duke.edu
K. Ranga R. Krishnan, MD 919-684-5616 krish001@acpub.duke.edu
Duke University Medical Centre

Zonisamide for weight reduction in obese patients

Rationale

Approximately 97 million adults in the United States are estimated to be overweight or obese, with a substantial increase of this epidemic in the recent years.[1, 2] With both conditions, there is a considerable increase in the prevalence of many comorbid illnesses including type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an increased risk of mortality from all causes.[3-5] Significant reduction of obesity-related illnesses and risk factors can occur with a modest (< 10%) weight reduction.[6] Although diet, exercise, behavior therapy and pharmacotherapy can be effective, many obese patients fail to achieve significant benefit from any given treatment modality, and the long-term outcome with most non-surgical treatments is often unsatisfactory.[7] In search of additional strategies for weight management in the clinically overweight and obese, we propose to conduct this preliminary investigation examining the efficacy and tolerability of zonisamide.

Zonisamide (Zonegran™) is an antiseizure drug with a sulfonamide chemical structure and unrelated to other antiseizure drugs. The drug is currently indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The drug's antiepileptic activity is believed to be mediated via dose-dependent blockade of sodium channels and T-type calcium channels. There is evidence that zonisamide may also protect neurons from free radical damage. In the US clinical trials in epilepsy, anorexia was reported in 13% of subjects receiving zonisamide. Although the following pharmacological actions of the zonisamide may not contribute to its antiseizure effects, these may be potentially be responsible for its anorexic effect. 1) carbonic anhydrase inhibiting (albeit weak) activity; and 2) dopaminergic and serotonergic activity at therapeutic doses.[8-10]

The present study seeks to gather preliminary information regarding the efficacy and tolerability of zonisamide in treating obesity.

Study Objectives

Primary

1 To examine whether zonisamide is more effective than placebo for weight loss in obese subjects prescribed a hypocaloric diet.

Secondary

1. To examine the effect of zonisamide on lipids, glucose, and body composition in obese subjects
2. To examine the tolerability and safety of zonisamide in the treatment of obesity

Study Endpoints

Primary

3. Mean change in absolute and percent body weight at 16 weeks

Secondary

4. Percentage of subjects with 5% weight loss
5. Absolute and percent change in body weight at each treatment visit
6. Change in waist circumference and/or body composition as assessed by DXA (optional)
7. Change in vital signs
8. Changes in total cholesterol, LDL, HDL, triglycerides and glucose at 16 weeks
9. Change in mood symptoms as measured by BDI
10. Incidence of treatment-emergent adverse effects

Study Design

This will be a 16-week, single-centre, randomised, double-blind, placebo-controlled, parallel-group study. Subjects, who meet all the inclusion and exclusion criteria, will be randomised in a 1:1 ratio to receive zonisamide or placebo for 16 weeks. Throughout the study, the subjects will adhere to a mildly hypocaloric diet (500 calories less than daily requirements based on the WHO algorithm). Follow-up visits after randomisation will be at weeks 1, 4, 8, 12 and 16.

Sample Size

The study will enroll 60 subjects, male and female, with the expectation that approximately 42 subjects will complete the full 16-week treatment.

Study Population

Inclusion criteria

1. Age 22-50
2. BMI of 30-44 kg/m2
3. Otherwise healthy as determined by the principal investigator

Exclusion criteria

1. Obesity of known endocrine aetiology, e.g., hypothyroidism, Cushing's syndromme, polycystic ovarian disease, etc.
2. Serious or unstable illness, e.g., significant cardiovascular disease, history of stroke, epilepsy, etc.
3. History of renal calculi
4. Significant hepatic or renal disease
5. Uncontrolled HTN
6. Current Type I diabetes mellitus or Type II DM on pharmacotherapy
7. Untreated or uncontrolled thyroid disease
8. Current use of other weight loss medications
9. Weight loss of >4kg in the past three months
10. Had surgery for obesity
11. Current major psychiatric disorder
12. Current alcohol or drug abuse
13. Current or recent use of medications that have the potential to 1) compromise study safety, or 2) pose difficulties in interpreting the study outcomes, e.g., medications known to significantly affect body weight
14. Current use of medications that significantly induce or inhibit P450 3A4 hepatic enzymes
15. Women of child-bearing potential, not adhering to an acceptable form of contraception
16. Pregnant or breast-feeding women
17. Subjects, judged to be inappropriate by the principal investigator, for other reasons such as risk of non-compliance or inability to follow study procedures

Study Drug and Dosing

Zonisamide is started at 100 mg qPM. Based on tolerability, the dose is titrated up as follows:
Weeks 3-4: 200 mg/d (100 mg b.i.d.)
Weeks 5-6: 300 mg/d (200 mg qAM and 100 mg qPM)
Weeks 7-8: 400 mg/d (200 mg b.i.d.)
Weeks 9-16: 600 mg/d (300 mg b.i.d.)

The dosing is flexible. Dose uptitration can be withheld and/or downtitrated, if necessary, depending on tolerability and the investigator's clinical judgment. Medication compliance is monitored via a log sheet given to the subjects and a review of the number of tablets dispensed and returned.

The study drug and matching placebo will be supplied by Elan pharmaceuticals. Duke investigational pharmacy will be responsible for randomisation and dispensing under blinded conditions.

Hypocaloric Diet

At randomisation visit, subjects will be instructed to follow a hypocaloric diet, representing a deficit of 500 kcal/d, based on the basal metabolic rate calculated by the WHO's revised equation with an adjustment for physical activity. They will keep daily records of food intake. Diet diaries will be provided.

Measurement and Evaluations

Efficacy assessments include:
Weight in examination gown without shoes on a calibrated electronic scale
Waist circumference
BMI
Beck Depression Inventory
Labs: lipid profile, glucose

Safety assessments include:
Adverse events
Clinical chemistry and haematology
Blood pressure and heart rate
Physical examination
Urinalysis
TSH at screening
Pregnancy test at screening

Data Analysis
Two subject populations will be considered for the efficacy endpoints: 1) an intent-to-treat (ITT) population, defined as all randomised subjects, and 2) a protocol-specific population, defined as the subset completing 16 weeks of treatment. Change in body weight at study exit will be evaluated via analysis of variance (ANOVA). Chochran-Mantel-Haenszel (CMH) tests, controlling for pooled centre, will be used to test differences in the proportions of responders between treatment groups. Linear mixed models with normal error structure can be used to support conclusions of the study, accommodating the repeated measurements (weeks 1, 4, 8, 12 and 16) and missing data. Each outcome, percent weight loss and actual weight loss, can be modeled with fixed effects due to baseline weight, treatment, week and treatment by week. A random intercept may be used for the subject-specific effect.

Adverse Events Monitoring
In placebo-controlled trials, the most frequent adverse effects of zonisamide were drowsiness (17% vs. 7%), ataxia (6% vs. 1%), and anorexia (13% vs. 6%).[11] Gastrointestinal problems, decreased spontaneity, slowing of mental activity, depression, agitation/irritability have also occurred at a slightly higher incidence than in the placebo group. Somnolence is more commonly observed at high doses of zonisamide. Patients will be advised not to drive a car or operate complex machinery until they have gained experience on zonisamide sufficient to determine whether it affects their performance. During the development of zonisamide in the US, 40 of 991 patients (4%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones. Patients will be advised to contact their physician immediately if they develop signs or symptoms that could indicate kidney stone, such as sudden back pain, abdominal pain, and/or blood in urine. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for kidney stones. Oligohydrosis and hyperthermia has been reported in Japan in pediatric patients with epilepsy taking zonisamide. There were no reported such cases in the US. Children will not studied in the proposed study. Skin rash led to the discontinuation of zonisamide in 2% of epilepsy patients in the randomised clinical trials during the drug development in the US and Europe. Patients will be advised to contact their physician immediately if a skin rash develops. Two confirmed cases of aplastic anaemia and confirmed case of agranulocytosis were reported in the first 11 years of marketing of zonisamide in Japan. There were no cases of aplastic anaemia and two confirmed cases of agranulocytosis in the US, European and Japanese development programmes. Because of the potential for rare haematological complications with zonisamide treatment, patients will be advised to contact their physician immediately if they develop a fever, sore throat, oral ulcers or easy bruising.

Informed consent, Ethics Review and Regulatory Consideration
The investigator agrees to take the above-mentioned responsibilities.

Strategic rationale / publication strategy
If zonisamide is superior to placebo in this pilot study, the information can be used for considering further studies in obesity. The data from this study can be presented at appropriate scientific meetings and published in appropriate scientific journals.

Investigator Experience
Dr. Gadde has recently reported the results of a preliminary investigation of bupropion in obesity using a similar design.[12] Weight loss in the bupropion group was significantly greater in the bupropion group compared to the placebo group at 8 weeks (6.2% vs. 1.6%; p=0.0002). The preliminary results have been presented at the recent annual meeting of the North American Association for Study of Obesity (NAASO) and the manuscript is currently under review. We have approximately 100 potential subjects who have called us in response to advertisements for other trials enrollment for which has been completed. These subjects in waiting could be quickly screened for the proposed study. We have the capability to conduct total body composition scans (DXA). Our group has a full-time research dietitian. Dr. Gadde is familiar with the procedures for seeking an IND exemption from the FDA.

References

1 Fiegal KM, Carroll MD, Kuczmarski RJ, Johnston CL. Overweight and obesity in the US: prevalence and trends, 1960-1994. *Int J Obesity.* 1998;22:39-47.
2 Mokdad AH, Serdula MK, dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. *JAMA.* 1999;282:1519-1522.
3 Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA.* 1999;282:1523-1529.
4 Calle EE, Tun MJ, Petreli JM, Rodriguez C, Heath Jr, CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 1999;341:1097-105.
5 Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. *JAMA.* 1999;282:1530-1538.
6 Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes.* 1992;6:397-415.
7 National Institutes of Health Technology Assessment Conference Panel. Methods for voluntary weight loss and control. *Ann Intern Med.* 1993;119:764-770.
8 Oommen KJ, Mathews S. Zonisamide: a new antiepileptic drug. *Clin Neuropharm.* 1999;22:192-200.
9 Mimaki. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther drug monitoring.* 1998;20:593-597.
10 Leppik. Zonisamide. *Epilepsia.* 1999;40 (suppl 5):S23-S29.
11 Product information for Zonegran (zonisamide) capsules. Elan Pharma. 2000
12 Gadde KM, Krishnan KRR, Drezner MK. Bupropion SR shows promise as an effective obesity treatment. *Obesity Res.* 1999;7(suppl. 1)51S.

Proposed Budget

Item	Start up	Screen	Baseline	wk 1	wk 4	wk 8	Wk 12	wk 16	Subtotal
Scr, Med Eval & PE		200							200
Labs & ECG		200							200
Follow-up			75	75	75	75	75	75	450
Dietitian			75		75	75	75	75	375
Weight, vitals		30	30	30	30	30	30	30	210
Supplies	50								50
Subtotal	50	430	180	105	180	180	180	180	1485
Patient costs	60 subjects x $1,485 = $89,100								
Screen failures	10 subjects x $430 = $4,300								
Inv. Pharmacy	8,000								
Coordinator	19,400 (50% salary plus fringe)								
PI support	18,400 (10% salary support plus fringe)								
TOTAL	$139,200 (direct costs)								

Institutional indirect costs = add 25%

Optional body composition scans (DXA), paired – 120 scans x 200 = 24,000 (60 subjects)

A sample size of 80 would provide greater power although 60 might be sufficient for a go-no go decision. The budget for additional 20 subjects would be approximately $30,000 without DXA or $38,000 with paired DXA.

Comments & Questions: The proposed dosing schedule is based on the product information guidelines. We seek your input in this regard.

EXHIBIT B

Proposal presented to Elan Pharma on the 7th September, 2000 by:
Kishore M. Gadde, MD 919-668-0208 gadde001@mc.duke.edu
K. Ranga R. Krishnan, MD 919-684-5616 krish001@acpub.duke.edu
Duke University Medical Centre
Revised and resubmitted on the 11th October, 2000

Zonisamide for weight reduction in obese patients

Rationale

Approximately 97 million adults in the United States are estimated to be overweight or obese, with a substantial increase of this epidemic in the recent years.[1, 2] With both conditions, there is a considerable increase in the prevalence of many comorbid illnesses including type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an increased risk of mortality from all causes.[3-5] Significant reduction of obesity-related illnesses and risk factors can occur with a modest (< 10%) weight reduction.[6] Although diet, exercise, behavior therapy and pharmacotherapy can be effective, many obese patients fail to achieve significant benefit from any given treatment modality, and the long-term outcome with most non-surgical treatments is often unsatisfactory.[7] In search of additional strategies for weight management in the clinically overweight and obese, we propose to conduct this preliminary investigation examining the efficacy and tolerability of zonisamide.

Zonisamide (Zonegran™) is an antiseizure drug with a sulfonamide chemical structure and unrelated to other antiseizure drugs. The drug is currently indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The drug's antiepileptic activity is believed to be mediated via dose-dependent blockade of sodium channels and T-type calcium channels. There is evidence that zonisamide may also protect neurons from free radical damage. In the US clinical trials in epilepsy, anorexia was reported in 13% of subjects receiving zonisamide. Although the following pharmacological actions of the zonisamide may not contribute to its antiseizure effects, these may be potentially be responsible for its anorexic effect. 1) carbonic anhydrase inhibiting (albeit weak) activity; and 2) dopaminergic and serotonergic activity at therapeutic doses.[8-10]

The present study seeks to gather preliminary information regarding the efficacy and tolerability of zonisamide in treating obesity.

Study Objectives

Primary

1. To examine whether zonisamide is more effective than placebo for weight loss in obese subjects prescribed a hypocaloric diet.

Secondary

1) To examine the effect of zonisamide on lipids, glucose, and body composition in obese subjects
2) To examine the tolerability and safety of zonisamide in the treatment of obesity
3) To gather 32-week data for subjects wishing to continue the study treatment after the first 16 weeks

Study Endpoints

Primary

1. Mean change in absolute and percent body weight at 16 weeks

Secondary

1) Percentage of subjects with 5% weight loss
2) Absolute and percent change in body weight at each treatment visit
3) Change in waist circumference and/or body composition as assessed by DXA (optional)
4) Change in vital signs
5) Changes in total cholesterol, LDL, HDL, triglycerides and glucose at 16 weeks
6) Change in mood symptoms as measured by BDI
7) Incidence of treatment-emergent adverse effects

Study Design

This will be a 16-week, single-centre, randomised, double-blind, placebo-controlled, parallel-group study. Subjects, who meet all the inclusion and exclusion criteria, will be randomised in a 1:1 ratio to receive zonisamide or placebo for 16 weeks. Throughout the study, the subjects will adhere to a mildly hypocaloric diet (500 calories less than daily requirements based on the WHO algorithm). Follow-up visits after randomisation will be at weeks 1, 4, 8, 12 and 16. Subjects wishing to continue

the study treatment will be maintained on the same treatment for an additional 16 weeks with visits at weeks 20, 24, 28, and 32.

Sample Size
The study will enroll 60 subjects, male and female, with the expectation that approximately 42 subjects will complete the full 16-week treatment. We estimate that approximately 30 subjects will opt to enter the additional 16-week continuation phase.

Study Population
Inclusion criteria
1. Age 21-50
2. BMI of 30-44 kg/m^2
3. Otherwise healthy as determined by the principal investigator

Exclusion criteria
1. Obesity of known endocrine aetiology, e.g., hypothyroidism, Cushing's syndromme, polycystic ovarian disease, etc.
2. Serious or unstable illness, e.g., significant cardiovascular disease, history of stroke, epilepsy, etc.
3. History of renal calculi
4. Significant hepatic or renal disease
5. Uncontrolled HTN
6. Current Type I diabetes mellitus or Type II DM on pharmacotherapy
7. Untreated or uncontrolled thyroid disease
8. Current use of other weight loss medications
9. Weight loss of >4kg in the past three months
10. Had surgery for obesity
11. Current major psychiatric disorder
12. Current alcohol or drug abuse
13. Current or recent use of medications that have the potential to 1) compromise study safety, or 2) pose difficulties in interpreting the study outcomes, e.g., medications known to significantly affect body weight
14. Current use of medications that significantly induce or inhibit P450 3A4 hepatic enzymes
15. Women of child-bearing potential, not adhering to an acceptable form of contraception
16. Pregnant or breast-feeding women
17. Subjects, judged to be inappropriate by the principal investigator, for other reasons such as risk of non-compliance or inability to follow study procedures

Study Drug and Dosing
Zonisamide is started at 50 mg qPM. Based on tolerability, the dose is titrated up as follows:
Week 2: 100 mg (50 mg b.i.d.)
Weeks 3-4: 200 mg/d (100 mg b.i.d.)
Weeks 5-6: 300 mg/d (200 mg qAM and 100 mg qPM)
Weeks 7-12: 400 mg/d (200 mg b.i.d.)
At the end of week 12, if at least 5% weight loss is not achieved, the dose can be further increased 600 mg/d (300 mg b.i.d.)

The dose at the completion of 16 weeks will remain the same during the additional 16-week continuation phase.

The dosing is flexible. Dose uptitration can be withheld and/or downtitrated, if necessary, depending on tolerability and the investigator's clinical judgment. Medication compliance is monitored via a log sheet given to the subjects and a review of the number of tablets dispensed and returned.

The study drug and matching placebo will be supplied by Elan pharmaceuticals. Duke investigational pharmacy will be responsible for randomisation and dispensing under blinded conditions.

Hypocaloric Diet
At randomisation visit, subjects will be instructed to follow a hypocaloric diet, representing a deficit of 500 kcal/d, based on the basal metabolic rate calculated by the WHO's revised equation with an adjustment for physical activity. They will keep daily records of food intake. Diet diaries will be provided.

Measurement and Evaluations
Efficacy assessments include:
Weight in examination gown without shoes on a calibrated electronic scale
Waist circumference, DXA
BMI
Beck Depression Inventory
Labs: lipid profile, glucose

Safety assessments include:
Adverse events
Clinical chemistry and haematology
Blood pressure and heart rate
Physical examination
Urinalysis
TSH at screening
Pregnancy test at screening

Data Analysis
Two subject populations will be considered for the efficacy endpoints: 1) an intent-to-treat (ITT) population, defined as all randomised subjects, and 2) a protocol-specific population, defined as the subset completing 16 weeks of treatment. Change in body weight at study exit will be evaluated via analysis of variance (ANOVA). Cochran-Mantel-Haenszel (CMH) tests, controlling for pooled centre, will be used to test differences in the proportions of responders between treatment groups. Linear mixed models with normal error structure can be used to support conclusions of the study, accommodating the repeated measurements (weeks 1, 4, 8, 12 and 16) and missing data. Each outcome, percent weight loss and actual weight loss, can be modeled with fixed effects due to baseline weight, treatment, week and treatment by week. A random intercept may be used for the subject-specific effect. Similar approaches will be utilised during the additional 16-week continuation phase. Principal analyses will be conducted on the first 16-week data.

Adverse Events Monitoring
In placebo-controlled trials, the most frequent adverse effects of zonisamide were drowsiness (17% vs. 7%), ataxia (6% vs. 1%), and anorexia (13% vs. 6%).[11] Gastrointestinal problems, decreased spontaneity, slowing of mental activity, depression, agitation/irritability have also occurred at a slightly higher incidence than in the placebo group. Somnolence is more commonly observed at high doses of zonisamide. Patients will be advised not to drive a car or operate complex machinery until they have gained experience on zonisamide sufficient to determine whether it affects their performance. During the development of zonisamide in the US, 40 of 991 patients (4%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones. Patients will be advised to contact their physician immediately if they develop signs or symptoms that could indicate kidney stone, such as sudden back pain, abdominal pain, and/or blood in urine. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for kidney stones. Oligohydrosis and hyperthermia has been reported in Japan in pediatric patients with epilepsy taking zonisamide. There were no reported such cases in the US. Children will not studied in the proposed study. Skin rash led to the discontinuation of zonisamide in 2% of epilepsy patients in the randomised clinical trials during the drug development in the US and Europe. Patients will be advised to contact their physician immediately if a skin rash develops. Two confirmed cases of aplastic anaemia and confirmed case of agranulocytosis were reported in the first 11 years of marketing of zonisamide in Japan. There were no cases of aplastic anaemia and two confirmed cases of agranulocytosis in the US, European and Japanese development programmes. Because of the potential for rare haematological complications with zonisamide treatment, patients will be advised to contact their physician immediately if they develop a fever, sore throat, oral ulcers or easy bruising.

Informed consent, Ethics Review and Regulatory Consideration
The investigator agrees to take the above-mentioned responsibilities.

Strategic rationale / publication strategy
If zonisamide is superior to placebo in this pilot study, the information can be used for considering further studies in obesity. The data from this study can be presented at appropriate scientific meetings and published in appropriate scientific journals.

Investigator Experience

Dr. Gadde has recently reported the results of a preliminary investigation of bupropion in obesity using a similar design.[12] Weight loss in the bupropion group was significantly greater in the bupropion group compared to the placebo group at 8 weeks (6.2% vs. 1.6%; p=0.0002). The preliminary results have been presented at the recent annual meeting of the North American Association for Study of Obesity (NAASO) and the manuscript is currently under review. We have approximately 100 potential subjects who have called us in response to advertisements for other trials enrollment for which has been completed. These subjects in waiting could be quickly screened for the proposed study. We have the capability to conduct total body composition scans (DXA). Our group has a full-time research dietitian. Dr. Gadde is familiar with the procedures for seeking an IND exemption from the FDA.

References

1. Fiegal KM, Carroll MD, Kuczmarski RJ, Johnston CL. Overweight and obesity in the US: prevalence and trends, 1960-1994. *Int J Obesity.* 1998;22:39-47.
2. Mokdad AH, Serdula MK, dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. *JAMA.* 1999;282:1519-1522.
3. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA.* 1999;282:1523-1529.
4. Calle EE, Tun MJ, Petreli JM, Rodriguez C, Heath Jr, CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med.* 1999;341:1097-105.
5. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual deaths attributable to obesity in the United States. *JAMA.* 1999;282:1530-1538.
6. Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes.* 1992;6:397-415.
7. National Institutes of Health Technology Assessment Conference Panel. Methods for voluntary weight loss and control. *Ann Intern Med.* 1993;119:764-770.
8. Oommen KJ, Mathews S. Zonisamide: a new antiepileptic drug. *Clin Neuropharm.* 1999;22:192-200.
9. Mimaki. Clinical pharmacology and therapeutic drug monitoring of zonisamide. *Ther drug monitoring.* 1998;20:593-597.
10. Leppik. Zonisamide. *Epilepsia.* 1999;40 (suppl 5):S23-S29.
11. Product information for Zonegran (zonisamide) capsules. Elan Pharma. 2000
12. Gadde KM, Krishnan KRR, Drezner MK. Bupropion SR shows promise as an effective obesity treatment. *Obesity Res.* 1999;7(suppl. 1)51S.

EXHIBIT C

Zonisamide in Obesity

Rationale

Approximately 97 million adults in the United States are estimated to be overweight or obese, with a substantial increase of this epidemic in the recent years.[1] With both conditions, there is a considerable increase in the prevalence of many comorbid illnesses including type 2 diabetes, coronary heart disease, hypertension, gallbladder disease, and osteoarthritis, with an increased risk of mortality from all causes.[2] Significant reduction of obesity-related illnesses and risk factors can occur with a modest (< 10%) weight reduction.[3] Although diet, exercise, behavior therapy and pharmacotherapy can be effective, many obese patients fail to achieve significant benefit from any given treatment modality, and the long-term outcome with most non-surgical treatments is often unsatisfactory. In search of additional strategies for weight management in the clinically overweight and obese, we propose to conduct this preliminary investigation examining the efficacy and tolerability of zonisamide.

Zonisamide (Zonegran™), currently indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, has shown anorexic effect in epilepsy trials. Although the following pharmacological actions of the zonisamide may not contribute to its antiseizure effects, these may be potentially be responsible for its anorexic effect. 1) carbonic anhydrase inhibiting (albeit weak) activity; and 2) dopaminergic and serotonergic activity at therapeutic doses.[4-7]

The present study seeks to gather preliminary information regarding the efficacy and tolerability of zonisamide in treating obesity.

Study Objectives

Primary

1. To examine whether zonisamide is more effective than placebo for weight loss in obese subjects prescribed a hypocaloric diet.

Secondary

1) To examine the effect of zonisamide on lipids, glucose, and body composition in obese subjects
2) To examine the tolerability and safety of zonisamide in the treatment of obesity
3) To gather 32-week data for subjects wishing to continue the study treatment after the first 16 weeks

Study Endpoints

Primary

1) Mean change in absolute and percent body weight at 16 weeks

Secondary

1) Percentage of subjects with 5% weight loss, 2) absolute and percent change in body weight at each treatment visit, 3) change in waist circumference, 4) body composition as assessed by DXA, 5) change in vital signs, 6) changes in total cholesterol, LDL, HDL, triglycerides and glucose, 7) changes in mood and quality of life as measured by BDI and IWQOL, respectively, and 8) incidence of treatment-emergent adverse effects

Study Design

This will be a 16-week, single-centre, randomised, double-blind, placebo-controlled, parallel-group study. Subjects, who meet all the inclusion and exclusion criteria, will be randomised in a 1:1 ratio to receive zonisamide or placebo for 16 weeks. Throughout the study, the subjects will adhere to a mildly hypocaloric diet (500 calories less than daily requirements based on the WHO algorithm). Follow-up visits after randomisation will be at weeks 2, 4, 8, 12 and 16. Subjects wishing to continue the study treatment will be maintained on the same treatment for an additional 16 weeks with visits at weeks 20, 24, 28, and 32.

Sample Size and Source of Subjects

The study will enroll 60 subjects, male and female, with the expectation that approximately 42 subjects will complete the full 16-week treatment. We estimate that approximately 30 subjects will opt to enter the additional 16-week continuation phase. The subjects will be recruited from the community via advertisements, posters and fliers, and from the pool of patients seeking treatment in the weigh management programs at DUMC. Informed consent will be obtained in accordance with HHS standards. A copy of the Consent Form is appended.

Study Population

Inclusion criteria

1) Age 21-50; 2) BMI of 30-44 kg/m^2; 3) Otherwise healthy as determined by the principal investigator

Exclusion criteria

1) Obesity of known endocrine aetiology, e.g., hypothyroidism, Cushing's syndromme, polycystic ovarian disease, etc; 2) Serious or unstable illness, e.g., significant cardiovascular disease, history of stroke, epilepsy, etc; 3) History of renal calculi; 4) Significant hepatic or renal disease; 5) Uncontrolled HTN; Current Type I diabetes mellitus or Type II DM on pharmacotherapy; 6) Untreated or uncontrolled thyroid disease; 7) Current use of other weight loss medications; 8) Weight loss of >4kg in the past three months; 9) Had surgery for obesity; 10) Current major psychiatric disorder; 11) Current alcohol or drug abuse; 12) Current or recent use of medications that have the potential to compromise study safety, or pose difficulties in interpreting the study outcomes, e.g., medications known to significantly affect body weight; 13) Current use of medications that significantly induce or inhibit P450 3A4 hepatic enzymes; 14) Allergy or hypersensitivity to sulfonamides; 15) Women of child-bearing potential, not

adhering to an acceptable form of contraception; 16) Pregnant or breast-feeding women; 17) Subjects, judged to be inappropriate by the principal investigator, for other reasons such as risk of non-compliance or inability to follow study procedures

Study Drug and Dosing
Zonisamide is started at 100 mg qd. Based on tolerability, the dose is titrated up as follows:
Weeks 3-4: 200 mg/d
Weeks 5-6: 300 mg/d
Weeks 7-12: 400 mg/d
At the end of week 12, if at least 5% weight loss is not achieved, the dose can be further increased to 600 mg/d.

The entire dose is given at bedtime. However, based on tolerability, a part of the daily dose may be given in the morning.

The dose at the completion of 16 weeks will remain the same during the additional 16-week continuation phase. The dosing is flexible. Dose uptitration can be withheld and/or downtitrated, if necessary, depending on tolerability and the investigator's clinical judgment. Medication compliance is monitored via a log sheet given to the subjects and a review of the number of tablets dispensed and returned. The study drug and matching placebo will be supplied by Elan pharmaceuticals. Duke investigational pharmacy will be responsible for randomisation and dispensing under blinded conditions.

Hypocaloric Diet
At randomisation visit, subjects will be instructed to follow a hypocaloric diet, representing a deficit of 500 kcal/d, based on the basal metabolic rate calculated by the WHO's revised equation with an adjustment for physical activity. They will keep daily records of food intake. Diet diaries will be provided.

Measurement and Evaluations
Efficacy assessments include: Weight (each visit) in examination gown without shoes on a calibrated electronic scale; and, BDI, IWQOL, DEXA, waist circumference, lipid profile and plasma glucose (Randomization visit, week 16 and week 32).

Safety assessments include: Adverse events, blood pressure and heart rate at every visit; physical examination, ECG, urinalysis, TSH, and serum pregnancy test (if applicable) at screening; CBC and chemistry at screening, week 16 and week 32 (or at study exit).

Data Analysis
Two subject populations will be considered for the efficacy endpoints: 1) an intent-to-treat (ITT) population, defined as all randomised subjects, and 2) a protocol-specific population, defined as the subset completing 16 weeks of treatment. Change in body weight at study exit will be evaluated via analysis of variance (ANOVA). Cochran-Mantel-Haenszel (CMH) tests, controlling for pooled centre, will be used to test differences in the proportions of responders between treatment groups. Linear mixed models with normal error structure can be used to support conclusions of the study, accommodating the repeated measurements (weeks 1, 4, 8, 12 and 16) and missing data. Each outcome, percent weight loss and actual weight loss, can be modeled with fixed effects due to baseline weight, treatment, week and treatment by week. A random intercept may be used for the subject-specific effect. Similar approaches will be utilised during the additional 16-week continuation phase. Principal analyses will be conducted on the first 16-week data.

Potential Hazards
Zonisamide: In placebo-controlled trials, the most frequent adverse effects of zonisamide were drowsiness (17% vs. 7%), and anorexia (13% vs. 6%).[11] Gastrointestinal problems, decreased spontaneity, slowing of mental activity, irritability, and ataxia have also occurred at a slightly higher incidence than in the placebo group. Somnolence is more commonly observed at high doses of zonisamide. Patients will be advised not to drive a car or operate complex machinery until they have gained experience on zonisamide sufficient to determine whether it affects their performance. During the development of zonisamide in the US, 40 of 991 patients (4%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones. Patients will be advised to contact their physician immediately if they develop signs or symptoms that could indicate kidney stone, such as sudden back pain, abdominal pain, and/or blood in urine. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for kidney stones. Skin rash led to the discontinuation of zonisamide in 2% of epilepsy patients in the randomised clinical trials during the drug development in the US and Europe. Patients will be advised to contact their physician immediately if a skin rash develops. Two confirmed cases of aplastic anaemia and confirmed case of agranulocytosis were reported in the first 11 years of marketing of zonisamide in Japan. There were no cases of aplastic anaemia and two confirmed cases of agranulocytosis in the US, European and Japanese development programmes. Because of the potential for rare haematological complications with zonisamide treatment, patients will be advised to contact their physician immediately if they develop a fever, sore throat, oral ulcers or easy bruising.

DEXA: The total amount of radiation from DEXA that the subject is exposed to is 1.5 mrem or less. This amount of exposure is less than 1% of the annual allowable occupational exposure level set by the National Committee on Radiation Protection.

Potential Benefits
There may be benefit to the subject in the form of weight loss, but such benefit is minimal because the maximum length of the study is 32 weeks. Research may gather information that may help obesity treatment in future.

Support
Unrestricted educational grant from Elan Pharma to Dr. Kishore Gadde. Study medication is also supplied by Elan Pharma.

References

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7. Product information for Zonegran (zonisamide) capsules. Elan Pharma. 2000

EXHIBIT D

learn new information regarding efficacy and safety of zonisamide in the treatment of obesity

Okada M, Kaneko S, Hirano T, et al. Effects of zonisamide on dopaminergic system. *Epilepsy Res*. 1995;22:193-205.

Okada M, Hirano T, Kawata Y, et al. Biphasic effects of zonisamide on serotonergic system in rat hippocampus. *Epilepsy Res*. 1999;34:187-197.

Objective: Based on the finding that zonisamide has serotonergic and dopaminergic effects and the observation that this novel anticonvulsant is associated with weight loss in epilepsy trials, we evaluated its short-term efficacy and safety in the treatment of obesity.

Method: 60 subjects were assigned to receive zonisamide or placebo (1:1 ratio) in a randomized, double-blind fashion for 16 weeks in addition to a slightly hypocaloric (500 kcal/day deficit) diet. Zonisamide dosing was flexible with a maximum of 600 mg/day.

Results: Using the available data for all randomized subjects with the last observation carried forward, the zonisamide group lost, on average, more bodyweight than the placebo group (5.98% vs. 1.09%; $p<0.0001$) during the 16-week period. 17/30 subjects in the zonisamide group and 3/30 in the placebo group lost 5% weight ($p<0.0003$). A random coefficient regression for weight change, with effects for age, race, gender, BMI, and percent body fat, estimated that zonisamide treatment over the 16-week study duration was associated with a 4.99 kg greater weight loss over placebo treatment ($p<0.0001$). Zonisamide was tolerated well with minimal side effects.

Conclusion: Zonisamide was significantly more effective than placebo as an adjunct to hypocaloric diet in the treatment of obesity.

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